REMARKS

In the office action, the Examiner maintained some of the objections and rejections raised in the previous office action while withdrawing others. The Examiner also raised a new obviousness rejection. The Examiner made the office action final. Applicants address the improper finality status of the office action and each of the objections and rejections maintained or raised by the Examiner below.

In view of the remarks below, applicants respectfully request the finality status of the office action be withdrawn and the merits of this patent application be reconsidered.

No extension of time is believed to be necessary and no fee is believed to be due in connection with this response. However, if any extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to Deposit Account No. 17-0055. No other fee is believed to be due in connection with this response. However, if any fee is due in this or any subsequent response, please charge the fee to the same Deposit Account No. 17-0055.

Improper Finality

Before addressing the substantive remarks provided in the office action of April 5, 2006, applicants note that the office action was made final. However, contrary to the Examiner's characterization, the new ground of rejection presented in the office action was not necessitated by applicants' amendments to the claims. The finality of the office action is premature. In particular, MPEP §706.07(a) states, "Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement."

The new ground of rejection in the office action is an obviousness rejection against claims 1, 15, and 37-43 set forth in the paragraph bridging pages 9 and 10 of the office action. The Examiner alleged that said claims are obvious over Roman et al. in view of Powell et al. or Lasker et al. because Roman et al. teach that cerebral vascular diseases can be treated by blocking the effects of 20-HETE and Powell et al. and Lasker et al. both teach that the HETE synthesis by CYP4A11 and CYP4F2 can be inhibited by an antibody to the respective enzyme. Applicants note that the subject matter in said claims that the Examiner believed to be obvious is not newly introduced by applicants' amendments but the same as that presented in originally filed claims 12 and 13. As pointed out in the previous response, originally filed claims 12 and 13 read on elected invention I(A) and should have been

examined. The Examiner apparently agreed to this point as pending claim 1 which incorporates the subject matter of originally filed claims 12 and 13 was examined. Therefore, the new obviousness rejection could have been raised against originally filed claims 12 and 13 and thus is not necessitated by applicants' amendments.

For the above reason, the finality of the office action of April 5, 2006 is premature under MPEP §706.07(a) and must be withdrawn under MPEP §§ 706.07(d) and 706.07(e). Accordingly, applicants respectfully request full and favorable consideration of the following remarks in support of patentability. However, should the Examiner find the reason unpersuasive, applicants request a subsequent office action (and not merely an Advisory Action) so that applicants will be afforded the required opportunities to respond to the new ground of rejection present in the office action of April 5, 2006.

Objections to the specification

The Examiner maintained the objection to the title of the application for not being descriptive of the elected invention, i.e., a method of treatment using HET0016. However, the Examiner did not respond to the applicants' arguments presented in the previous response, in which applicants cited MPEP § 809 to explain why the title of the application is appropriate. Applicants do not understand why the objection is maintained in view of the arguments and respectfully request clarification as to why the arguments are not persuasive. In this regard, applicants note that MPEP 707.07(f) provides that "[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it."

Objections to the claims

The Examiner maintained the objection to the claim set for not beginning with a sentence of which the claims are an object. Applicants do not understand why the objection is maintained because, as argued in the previous response, the claim set begins with the sentence "WE CLAIM..." of which the claims are an object. Clarification on why the objection is maintained is respectfully requested. In this regard, applicants note that MPEP 707.07(f) provides that "[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it."

Claim rejections under 35 U.S.C. §101

The Examiner rejected claims 1, 7-11, 15, 17, and 37-44 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-13, 19-22, and 24-28 of U.S. Application No. 10/986,695. Applicants believe that the rejection is still a provisional rejection because U.S. Application No. 10/986,695 is still pending (see MPEP § 804II.B. ¶8.34 Examiner Note:2 and ¶8.35). Applicants stand ready to address the rejection should it be maintained as an actual rejection.

Enablement rejection under 35 U.S.C. §112-first paragraph

The Examiner rejected claims 1, 7-11, 15, 17, and 37-44 for failing to meet the enablement requirement, alleging that the specification does not enable all methods of treating cerebral vascular disease using any compound that decreases the activity of any CYP4A or CYP4F 20-HETE synthesizing enzyme. In particular, the Examiner alleged that the specification fails to support reasons (A)-(H) as set forth on page 3 of the office action. Applicants traverse the rejection below.

With regard to reason (A) on page 3 of the office action, applicants note that 20-HETE synthesizing enzymes that are of the CYP4A or CYP4F subclass are known in the art by their amino acid sequences and therefore a skilled artisan is familiar with their structure.

With regard to reasons (B)-(E) on page 3 of the office action, applicants note that identifying new 20-HETE synthesizing enzyme inhibitors either by testing new compounds or modifying existing inhibitors is not part of the invention. The present invention only calls for the use of known inhibitors or those that will become known, independent of the present invention, in the future. If someone else will find ways to modify existing 20-HETE synthesizing enzyme inhibitors that can maintain or enhance the inhibition activity, that is future technology and the Federal Circuit has held that the enablement requirement is not applicable to future technologies. *Chiron Corporation v. Genentech Inc.*, 363 F.3d 1247 (Fed. Cir. 2004).

In replying to applicants' arguments that the enablement is not applicable to future technologies, the Examiner pointed out that *Chiron Corporation v. Genentech Inc.* stated (Reply(B) on page 5 of the office action):

> Nascent technology must be enabled with a specific and useful teaching. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the

patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology.

This statement is acknowledged. However, this statement was made in *Chiron Corporation v. Genentech Inc.* with respect to the lack of disclosure in the specification on how to make chimeric antibodies, which was new technology at the time the applications were filed and few people knew how to make them at the time. This is not the case in the present application. The known 20-HETE synthesizing enzyme inhibitors are either commercially available or can be readily made with routine, mature technology.

In replying to applicants arguments that the application provides numerous examples of known 20-HETE synthesizing enzyme inhibitors and this is sufficient to enable the claims at issue under the U.S. patent law (citing *In re Herschler*, 591 F.2d 693 (CCPA 1979) and *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 928 (Fed. Cir. 2004)) and as recognized by the U.S. Patent and Trademark Office (citing U.S. Patent Nos. 6,756,399; 6,455,541; 6,376,528; 6,191,169; 6,187,756; 6,136,839; and 5,928,654), the Examiner replied that the specification teaches the structure of a single inhibitor of a single member of all CYP4F enzymes and the structure of a single inhibitor of a single member of all CYP4A enzymes and the prior art teaches the structure of a single inhibitor of two different members of the CYP4A subfamily. See Reply(A) on pages 4 and 5 and Reply(C) on page 6 of the office action.

In response, applicants respectfully note that the gist of the invention resides in the recognition that the four particular cerebral vascular diseases recited in the claims are associated with an increase in the 20-HETE level and that inhibitors of the group of enzymes of the CYP4A and CYP4F families are effective in treating the diseases. In this regard, the application provides a number of examples of the inhibitors for said group of enzymes (HET0016, 17-ODYA, dibromododecenyl methylsulfimide, 1-aminobenzotriazole, and miconazole) and a skilled artisan is familiar with others. With respect to the Examiner's statement that neither 17-ODYA nor miconazole is a specific inhibitor of CYP4A or CYP4F, they are nevertheless inhibitors of at least a member of the enzyme group as they inhibit 20-HETE synthesis in microsomal assays. The fact that they may also inhibit other enzymes do not change the fact that they inhibit 20-HETE synthesis and may be used to treat cerebral vascular diseases such as shown by Example 2 of the application for 17-ODYA. Therefore, the claims at issue are enabled with respect to the inhibitors of said group of enzymes as a number of examples of the inhibitors of the group are disclosed and a skilled artisan is familiar with others.

With regard to reason (F) on page 3 of the office action, applicants first note that, as discussed above, identifying ways to modify known 20-HETE synthesizing enzyme inhibitors to maintain or enhance the inhibition activity is not part of the invention and thus is not required to enable the invention. In addition, once a compound is discovered as useful for treating a certain disease in an animal model, it is routine to test various formulations for various routes of administration. Specific guidance is available in the art. *See e.g.*, Remington's Pharmaceutical Sciences, 16th, 18th, and 19th eds., Mack Publishing, Easton Pa. (1980, 1990, & 1995). With respect to the route of administration in particular, the Examiner has not provided any evidence to suggest that a particular route of administration does not work. The evidence is to the contrary. All routes that have been tested by applicants as provided in the application worked. Even if it is scientifically sound to doubt the other, non-exemplified administrative routes, the claimed invention is nevertheless enabled because the claims may encompass inoperable subject matter. In this regard, the enablement standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *See* MPEP 2164.08(b), citing *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). If the experimentation involved is merely routine, a considerable amount is permissible. *See In re Wands*, 858 F. 2d 731 (Fed. Cir. 1988). Applicants respectfully submit that a skilled artisan can simply administer a 20-HETE synthesizing enzyme inhibitor such as HET0016 via a particular route using one of the well known rat models provided in the application and will be able to determine whether the route is effective. Such an experiment is merely routine. Therefore no more effort than that is normally required is involved in the determination of the effectiveness of a particular route of administration.

Lastly, applicants note that clinical data is not required to enable an invention. As the Federal Circuit has recognized in *In re Brana*, 34 USPQ2d 1437, 1442 (Fed. Cir. 1995):

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

With regard to reason (G) on page 3 of the office action, applicants note that the claims at issue are directed to a method of treating one of the four particular cerebral vascular diseases recited in the claims while Hoagland et al. 2003 is concerned with hypertension. Clarification on why Hoagland et al. 2003 renders the present invention not enabled is respectfully requested.

With regard to reason (H) on page 3 of the office action, applicants refer to all arguments for the enablement rejection presented above to submit that the claims at issue are enabled.

Written description rejection under 35 U.S.C. §112-first paragraph

The Examiner rejected claims 1, 7-11, 15, 17, and 37-44 for failing to satisfy the written description requirement, alleging that the specification does not reasonably describe the genus of all methods of treating the recited cerebral vascular diseases using any compound that decreases the activity of any CYP4A or CYP4F 20-HETE synthesizing enzyme. Applicants traverse the rejection below.

The gist of invention resides in the inventors' recognition that the four particular cerebral vascular diseases recited in the claims are associated with an increase in the 20-HETE level (*see e.g.*, Example 1 in the application). The inventors further showed, using HET0016 and 17-ODYA as examples, that inhibiting 20-HETE synthesis are effective in treating the diseases (*see* Examples 1 and 2 in the application). In this regard, applicants provide a number of examples of 20-HETE synthesis inhibitors in the application (HET0016, 17-ODYA, dibromododecenyl methylsulfimide, 1-aminobenzotriazole, and miconazole) and a skilled artisan is familiar with others. As also provided in the application, it is well established in the art that enzymes of the CYP4A and CYP4F families catalyze the synthesis of 20-HETE (*see e.g.*, paragraph [0005] on page 2 of the application) and a skilled artisan understands that the above inhibitors inhibit 20-HETE synthesis by inhibiting one of the CYP4A and CYP4F family members. Accordingly, a skilled artisan appreciates from what is disclosed in the application that inhibitors of the enzymes of the CYP4A and CYP4F families, with which he or she is familiar, can be used to treat the four cerebral vascular diseases recited in the claims. Therefore, the written description requirement is satisfied.

Claim rejections under 35 U.S.C. §102

1. Alonso-Galicia et al. 1999

The Examiner rejected claims 1, 17, 37, 39, and 41 as being anticipated by Alonso-Galicia et al. 1999 as evidenced by Wang et al., alleging that Alonso-Galicia et al. 1999 teaches that intracerebroventricular injection of dibromododecenyl methylsulfimide (DDMS) reduces cerebral blood flow (Fig. 7) and that Wang et al. teach that DDMS inhibits CYP4A1 and CYP4A3. Applicants traverse the rejection below.

As noted by the Examiner in the office action and pointed out by applicants in the previous response, Alonso-Galicia et al. 1999 teach that intracerebroventricular injection of DDMS reduces "cerebral blood flow increase" (caused by the short acting NO donor MAHMA nonoate). However, the claims at issue involve the use of a 20-HETE synthesizing enzyme inhibitor to increase or prevent a decrease in cerebral blood flow, which is completely different from what Alonso-Galicia et al. taught. Therefore, claims 1, 17, 37, 39, and 41 are not anticipated by Alonso-Galicia et al. as evidenced by Wang et al.

Applicants note that the above arguments have been presented in the previous response. However, the Examiner did not respond to the arguments. If the rejection is to be maintained, applicants respectfully request explanation as to why the arguments are not persuasive. In this regard, applicants note that MPEP 707.07(f) provides that "[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it."

2. Su et al. 1999

The Examiner rejected claims 1, 37, 39, and 41 as being anticipated by Su et al. 1999 as evidenced by Fotherby et al. 1997 or Schmidt et al. 2000. In particular, the Examiner alleged that Su et al. 1999 teach that 1-aminobenzotriazole inhibits 20-HETE synthesis (Fig. 1), reduces blood pressure (Fig. 9), and decreases the expression of the HETE synthesizing enzyme CYP4A1, while Fotherby et al. and Schmidt et al. demonstrate that it is well known in the art that reducing blood pressure is an effective way for treating cerebral vascular diseases. Applicants traverse the rejection below.

Su et al. 1999 teach that 1-aminobenzotriazole is a 20-HETE inhibitor and it was able to lower blood pressure in a strain of spontaneously hypertensive rats (SHR). However, Su et al. 1999 do not show whether 1-aminobenzotriazole can lower blood pressure in normotensive rats. In fact, in subsequent studies with normotensive rats, others have shown that 1-aminobenzotriazole caused hypertension when the rats were fed high salt diet and

lowered blood pressure when the rats were fed low salt diet (Hoagland et al., Hypertension 42:669-673, 2003). In the same normotensive rats, HET0016 either caused hypertension or did not change the blood pressure (Hoagland et al., Hypertension 42:669-673, 2003).

Furthermore, it is not true that lowering blood pressure is an effective treatment for occlusive stroke and hemorrhagic stroke. Fotherby et al. and Schmidt et al. teach that chronic hypertension increases the risk for stroke by promoting arteriolosclerosis and narrowing the cerebral arteries. However, they do not establish that lowering blood pressure is an effective treatment for stroke. Fotherby et al. noted that "[t]he risks and benefits of antihypertensive therapy in the large number of older and frailer stroke patients commonly seen in our hospital remain largely unresolved" (page 625, right column, lines 9-12). Schmidt et al. only mention that hypertension is associated with stroke but do not provide that lowering blood pressure is an effective treatment. In fact, lowering blood pressure with systemic vasodilators or antihypertensive drugs are counterindicated in the treatment of both occlusive and hemorrhagic stroke. In both instances the goal is to increase blood flow to vessels that are occluded (occlusive stroke) or leaking (hemorrhagic stroke). In the case of occlusive stroke, flow can be restored by raising systemic pressure to the bed to push flow through the occlusion or increase collateral flow. Current treatment emphasizes triple H therapy, i.e., hypervolemia, hypertension, and hemodilation to maintain blood flow to the at risk region of the brain (Treggiari MM et al. J. Neurosurg. 99:978-984, 2003). Volume expansion is used to enhance cardiac output and reduce vasoconstriction. Hemodilution reduces the viscosity of the blood and hypertension driven by inotrophic drugs like dobutamine is used to maintain adequate perfusion.

For the above reasons, Su et al. 1999 together with Fotherby et al. and Schmidt et al. do not anticipate the claims at issue.

Applicants note that the above arguments have been presented in the previous response. However, the Examiner did not respond to the arguments. If the rejection is to be maintained, applicants respectfully request explanation as to why the characterization of the relevant references by applicants are wrong and the arguments not persuasive. In this regard, applicants note that MPEP 707.07(f) provides that "[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it."

Claim rejections under 35 U.S.C. §103

1. Roman et al. 1999 (WO 99/43310) in view of Frisbee et al. 2000

The Examiner rejected claims 1, 15, 37, and 39-41 as being obvious over Roman et al. 1999 (WO 99/43310) in view of Frisbee et al. 2000. In particular, the Examiner alleged that Roman et al. disclosed that cerebral vascular diseases can be treated by blocking the effect of 20-HETE and Frisbee et al. disclosed that 17-ODYA and dibromododecenyl methylsulfimide inhibit 20-HETE production and P450 -hydroxylase (a 20-HETE synthesizing enzyme of the CYP4A subclass). Applicants traverse the rejection below.

Roman et al. 1999 disclosed the use of 20-HETE antagonists, not a 20-HETEsynthesizing enzyme inhibitor, to treat cerebral vascular diseases (page 5, line 4). 20-HETE antagonists block the 20-HETE receptor while 20-HETE synthesizing enzyme inhibitors inhibit the synthesis of 20-HETE. As shown in the application, hemorrhagic stroke is associated with an elevation in the formation of 20-HETE in the cerebral circulation and that a 20-HETE synthesizing enzyme inhibitor could be given to treat the acute fall in cerebral blood flow and the vasospasm caused by hemorrhagic stroke. The same thing is true for occlusive stroke. The levels of 20-HETE in the brain can increase because of increased synthesis or the release of preformed 20-HETE stored in membrane phospholipid pools in (i) blood elements such as white blood cells and platelets, (ii) neural tissues such as brain neurons, (iii) vascular tissues such as vascular myocytes, and (iv) circulates bound to plasma proteins. While a 20-HETE antagonist is effective regardless of what causes the increase in 20-HETE level because it blocks the downstream 20-HETE receptor, a 20-HETE synthesis inhibitor will not be effective if 20-HETE is released from storage pools. Neither Roman et al. 1999 nor Frisbee et al. disclose or suggest that the increase in 20-HETE level in hemorrhagic or occlusive stroke is caused by increased synthesis but not release from storage pools. Therefore, it is not obvious that a 20-HETE synthesizing enzyme inhibitor will work. At the most, the present invention might be merely obvious to try, but without reasonable likelihood of success.

Applicants note that the above arguments have been presented in the previous response. However, the Examiner did not respond to the arguments. If the rejection is to be maintained, applicants respectfully request explanation as to why the arguments are not persuasive. In this regard, applicants note that MPEP 707.07(f) provides that "[w]here the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it."

2. Roman et al. in view of Powell et al or Lasker et al.

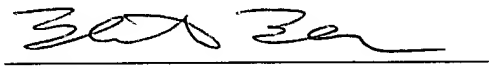
The Examiner rejected claims 1, 15, and 37-43 as being obvious over Roman et al. 1999 (WO 99/43310) in view of Powell et al. 1998 or Lasker et al. 2000. In particular, the Examiner alleged that Roman et al. disclosed that cerebral vascular diseases can be treated by blocking the effect of 20-HETE and both Powell et al. 1998 and Lasker et al. 2000 teach that the HETE synthesis by CYP4A11 and CYP4F2 can be inhibited by an antibody to the respective enzyme. In the Examiner's opinion, it would have been obvious to administer the antibodies of Powell et al. 1998 or Lasker et al. 2000 intravenously for the treatment of cerebral vascular disease and motivation to do so is provided by Powell et al. 1998 or Lasker et al. 2000 wherein they state that elevated 20-HETE levels, via CYP4A11 and/or CYP4F2, contributes to hypertension and vasoconstriction, which are well known in the art to be causative factors and/or exacerbate cerebral vascular disease. The Examiner further asserts that the expectation of success is high because the antibodies taught by Powell et al. 1998 and Lasker et al. 2000 are known inhibitors of 20-HETE synthesis. Applicants traverse the rejection below.

As already discussed above, Roman et al. 1999 disclosed the use of 20-HETE antagonists, not a 20-HETEsynthesizing enzyme inhibitor, to treat cerebral vascular diseases (page 5, line 4). 20-HETE antagonists block the 20-HETE receptor while 20-HETE synthesizing enzyme inhibitors inhibit the synthesis of 20-HETE. As discussed above, the gist of invention resides in the inventors' recognition that the four particular cerebral vascular diseases recited in the claims are associated with an increase in the 20-HETE level (*see e.g.*, Example 1 in the application). The levels of 20-HETE in the brain can increase because of increased synthesis or the release of preformed 20-HETE stored in membrane phospholipid pools in (i) blood elements such as white blood cells and platelets, (ii) neural tissues such as brain neurons, (iii) vascular tissues such as vascular myocytes, and (iv) circulates bound to plasma proteins. While a 20-HETE antagonist is effective regardless of what causes the increase in 20-HETE level because it blocks the downstream 20-HETE receptor, a 20-HETE synthesis inhibitor will not be effective if 20-HETE is released from storage pools. Neither Roman et al. 1999 nor Powell et al./Lasker et al. disclose or suggest that the increase in 20-HETE level in hemorrhagic or occlusive stroke is caused by increased synthesis but not release from storage pools. Therefore, it is not obvious that a 20-HETE synthesizing enzyme inhibitor will work. At the most, the present invention might be merely obvious to try, but without reasonable likelihood of success. Accordingly, claims 1, 15, and 37-43 are not obvious over Roman et al. in view of Powell et al. or Lasker et al.

Conclusion

Having addressed each issue raised by the Examiner, claims 1, 7-11, 15, 17, and 37-43 are believed to be in condition for allowance and a Notice of Allowance is respectfully requested. Should any issues remain outstanding, the Examiner is invited to contact the undersigned at the telephone number appearing below if such would advance the prosecution of this application.

Respectfully submitted,



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